10/556,668

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=> d his

     (FILE 'HOME' ENTERED AT 10:14:24 ON 05 NOV 2007)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 10:14:54 ON 05 NOV 2007
L1        134033 S "BCL-2"
L2         36036 S ANTI(W)APOPTOTIC
L3         14816 S L1 AND L2
L4        155793 S "BCL###"
L5         14816 S L3 AND L4
L6        141558 S "BCL-XL" OR "BCL-2" OR "BCL-W"
L7         14816 S L5 AND L6
L8           245 S DIMER? AND L7
L9            25 S LIGAND? AND L8
L10           10 DUP REM L9 (15 DUPLICATES REMOVED)
                 E GENESTE O/AU
L11           54 S E5
                 E HICKMAN J/AU
L12          264 S E3
                 E BENNETT R/AU
L13          999 S E3
                 E RAIN J C/AU
L14           87 S E3
L15         1399 S L11 OR L12 OR L13 OR L14
L16            0 S L8 AND L15
L17           25 S L1 AND L15
L18           10 DUP REM L17 (15 DUPLICATES REMOVED)
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NEWS	2	JUL 02	LMEDLINE coverage updated
NEWS	3	JUL 02	SCISEARCH enhanced with complete author names
NEWS	4	JUL 02	CHEMCATS accession numbers revised
NEWS	5	JUL 02	CA/CAplus enhanced with utility model patents from China
NEWS	6	JUL 16	CAplus enhanced with French and German abstracts
NEWS	7	JUL 18	CA/CAplus patent coverage enhanced
NEWS	8	JUL 26	USPATFULL/USPAT2 enhanced with IPC reclassification
NEWS	9	JUL 30	USGENE now available on STN
NEWS	10	AUG 06	CAS REGISTRY enhanced with new experimental property tags
NEWS	11	AUG 06	FSTA enhanced with new thesaurus edition
NEWS	12	AUG 13	CA/CAplus enhanced with additional kind codes for granted patents
NEWS	13	AUG 20	CA/CAplus enhanced with CAS indexing in pre-1907 records
NEWS	14	AUG 27	Full-text patent databases enhanced with predefined patent family display formats from INPADOCDB
NEWS	15	AUG 27	USPATOLD now available on STN
NEWS	16	AUG 28	CAS REGISTRY enhanced with additional experimental spectral property data
NEWS	17	SEP 07	STN AnaVist, Version 2.0, now available with Derwent World Patents Index
NEWS	18	SEP 13	FORIS renamed to SOFIS
NEWS	19	SEP 13	INPADOCDB enhanced with monthly SDI frequency
NEWS	20	SEP 17	CA/CAplus enhanced with printed CA page images from 1967-1998
NEWS	21	SEP 17	CAplus coverage extended to include traditional medicine patents
NEWS	22	SEP 24	EMBASE, EMBAL, and LEMBASE reloaded with enhancements
NEWS	23	OCT 02	CA/CAplus enhanced with pre-1907 records from Chemisches Zentralblatt
NEWS	24	OCT 19	BEILSTEIN updated with new compounds

NEWS EXPRESS 19 SEPTEMBER 2007: CURRENT WINDOWS VERSION IS V8.2, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 19 SEPTEMBER 2007.

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NEWS LOGIN	Welcome Banner and News Items
NEWS IPC8	For general information regarding STN implementation of IPC 8

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FILE 'HOME' ENTERED AT 10:14:24 ON 05 NOV 2007

=> file medline embase biosis biotechds scisearch hcaplus ntis lifesci
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                                                           ENTRY    SESSION
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FILE 'LIFESCI' ENTERED AT 10:14:54 ON 05 NOV 2007
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=> s "Bcl-2"
L1      134033 "BCL-2"

=> s anti(w)apoptotic
L2       36036 ANTI(W) APOPTOTIC

=> s l1 and l2
L3       14816 L1 AND L2

=> s "bcl###"
L4      155793 "BCL###"

=> s l3 and l4
L5       14816 L3 AND L4

=> s "BCL-XL" or "Bcl-2" or "Bcl-W"
L6      141558 "BCL-XL" OR "BCL-2" OR "BCL-W"

=> s l5 and l6
L7       14816 L5 AND L6

=> s dimer? and l7
L8         245 DIMER? AND L7

=> s lidan? and l8
<------User Break------>
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=> s ligand? and l8
L9          25 LIGAND? AND L8

=> dup rem l9
PROCESSING COMPLETED FOR L9
L10         10 DUP REM L9 (15 DUPLICATES REMOVED)

=> d 1-10 ibib ab

L10  ANSWER 1 OF 10  SCISEARCH  COPYRIGHT (c) 2007 The Thomson Corporation  on
     STN                                                    DUPLICATE 1
ACCESSION NUMBER:    2007:125324  SCISEARCH
THE GENUINE ARTICLE: 125ZX
TITLE:               Heat-induced dimerization of BCL-x(L)
                     through alpha-helix swapping
AUTHOR:              Denisov, Alexey Yu.; Sprules, Tara; Fraser, James; Kozlov,
                     Guennadi; Gehring, Kalle (Reprint)
CORPORATE SOURCE:    McGill Univ, Dept Biochem, 3655 Promenade Sir William
                     Osler, Montreal, PQ H3G 1Y6, Canada (Reprint); McGill
                     Univ, Dept Biochem, Montreal, PQ H3G 1Y6, Canada; McGill
                     Univ, Quebec Eastern Canada High Field NMR Facil,
                     Montreal, PQ H3G 1Y6, Canada
                     kalle.gehring@mcgill.ca
COUNTRY OF AUTHOR:   Canada
SOURCE:              BIOCHEMISTRY, (23 JAN 2007) Vol. 46, No. 3, pp. 734-740.
                     ISSN: 0006-2960.
PUBLISHER:           AMER CHEMICAL SOC, 1155 16TH ST, NW, WASHINGTON, DC 20036
                     USA.
DOCUMENT TYPE:       Article; Journal
LANGUAGE:            English
REFERENCE COUNT:     51
ENTRY DATE:          Entered STN: 8 Feb 2007
                     Last Updated on STN: 8 Feb 2007
                    *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*
AB       The dimerization of anti-apoptotic
     BCL-x(L) by three-dimensional domain swapping has recently been
     discovered at alkaline pH; however, the high energetic barrier between the
     dimer and monomer forms of BCL-x(L) prevents them from
     interconverting at room temperature and neutral pH.  Here, we demonstrate
     that BCL-x(L) dimers can be easily prepared by heating
     concentrated protein above 50 degrees C.  The 38 kDa BCL-x(L)
     dimer was fully characterized by multi-resonance nuclear magnetic
     resonance (NMR) spectroscopy, and the mechanism of dimerization
     by alpha-helix swapping was confirmed.  Dimerization strongly
     affects the NMR signals from the turn between helices alpha 5 and alpha 6
     of BCL-x(L) and a portion of the long loop between helices alpha
     1 and alpha 2.  Measurements of residual dipolar couplings demonstrate
     that the solution structure of the BCL-x(L) dimer is
     very close to the crystal structure.  Dimer formation does not
     prevent tight binding of ligands to the hydrophobic cleft of
     BCL-x(L); however, binding of a BID BH3-peptide or a polyphenol
     drug, gossypol, to BCL-x(L) significantly slowed monomer-
     dimer interconversion and is an example of the control of
     BCL protein oligomerization by ligand binding.

L10  ANSWER 2 OF 10  HCAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:        2005:134640  HCAPLUS
DOCUMENT NUMBER:         142:276101
TITLE:                   α-Melanocyte-stimulating Hormone Protects from
                         Ultraviolet Radiation-induced Apoptosis and DNA Damage
AUTHOR(S):               Boehm, Markus; Wolff, Ilka; Scholzen, Thomas E.;
                         Robinson, Samantha J.; Healy, Eugene; Luger, Thomas
                         A.; Schwarz, Thomas; Schwarz, Agatha
```

CORPORATE SOURCE: Department of Dermatology and the Ludwig Boltzmann Institute for Cell Biology and Immunobiology of the Skin, Univ. Muenster, Muensterton, D-48149, Germany
SOURCE: Journal of Biological Chemistry (2005), 280(7), 5795-5802
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB UV radiation is a well established epidemiol. risk factor for malignant melanoma. This observation has been linked to the relative resistance of normal melanocytes to UV B (UVB) radiation-induced apoptosis, which consequently leads to accumulation of UVB radiation-induced DNA lesions in melanocytes. Therefore, identification of physiol. factors regulating UVB radiation-induced apoptosis and DNA damage of melanocytes is of utmost biol. importance. We show that the neuropeptide α-MSH (α-MSH) blocks UVB radiation-induced apoptosis of normal human melanocytes in vitro. The anti-apoptotic activity of α-MSH is not mediated by filtering or by induction of melanin synthesis in melanocytes. α-MSH neither leads to changes in the cell cycle distribution nor induces alterations in the expression of the apoptosis-related proteins Bcl2, Bclx, Bax, p53, CD95 (Fas/APO-1), and CD95L (FasL). In contrast, α-MSH markedly reduces the formation of UVB radiation-induced DNA damage as demonstrated by reduced amts. of cyclobutane pyrimidine dimers, ultimately leading to reduced apoptosis. The reduction of UV radiation-induced DNA damage by α-MSH appears to be related to induction of nucleotide excision repair, because UV radiation-mediated apoptosis was not blocked by α-MSH in nucleotide excision repair-deficient fibroblasts. These data, for the first time, demonstrate regulation of UVB radiation-induced apoptosis of human melanocytes by a neuropeptide that is physiol. expressed within the epidermis. Apart from its ability to induce photoprotective melanin synthesis, α-MSH appears to exert the capacity to reduce UV radiation-induced DNA damage and, thus, may act as a potent protection factor against the harmful effects of UV radiation on the genomic stability of epidermal cells.

REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 3 OF 10 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2006038687 IN-PROCESS
DOCUMENT NUMBER: PubMed ID: 16215673
TITLE: Sensitization of prostate carcinoma cells to Apo2L/TRAIL by a Bcl-2 family protein inhibitor.
AUTHOR: Ray S; Bucur O; Almasan A
CORPORATE SOURCE: Department of Cancer Biology, Lerner Research Institute, The Cleveland Clinic Foundation, Cleveland, Ohio, 44195.
SOURCE: Apoptosis : an international journal on programmed cell death, (2005 Dec) Vol. 10, No. 6, pp. 1411-8.
Journal code: 9712129. ISSN: 1360-8185.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: NONMEDLINE; IN-DATA-REVIEW; IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 24 Jan 2006
Last Updated on STN: 12 Dec 2006

AB Overexpression of anti-apoptotic Bcl-2 family proteins may play an important role in the aggressive behavior of prostate cancer cells and their resistance to therapy. The Bcl-2 homology 3 domain (BH3) is a uniquely important functional element within the pro-apoptotic class of the Bcl-2-related proteins, mediating their ability to dimerize

with other Bcl-2-related proteins and promote apoptosis. The BH3 inhibitors (BH3Is) function by disrupting the interactions mediated by the BH3 domain between pro- and anti-apoptotic members of the Bcl-2 family and liberating more Bax/Bak to induce mitochondrial membrane permeabilization. LNCaP-derived C4-2 human prostate cancer cells are quite resistant to non-tagged, human recombinant soluble Apo2 ligand [Apo2L, also Tumor necrosis factor (TNF)-related apoptosis-inducing ligand, TRAIL], a tumor specific drug that is now in clinical trials. However, when Apo2L/TRAIL was combined with the Bcl-xL inhibitor, BH3I-2', it induced apoptosis synergistically through activation of Caspase-8 and the proapoptotic Bcl-2 family member Bid, resulting in the activation of effector Caspase-3 and proteolytic cleavage of Poly(ADP-ribose) polymerase, events that were blocked by the pan-caspase inhibitor zVAD-fmk. Our data indicate that, in combination with the BH3 mimetic, BH3I-2', Apo2L/TRAIL synergistically induces apoptosis in C4-2 human prostate cancer cells through both the extrinsic and intrinsic apoptotic pathways.

L10 ANSWER 4 OF 10 MEDLINE on STN
ACCESSION NUMBER: 2003537477 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12963734
TITLE: Central role of Fas-associated death domain protein in apoptosis induction by the mitogen-activated protein kinase kinase inhibitor CI-1040 (PD184352) in acute lymphocytic leukemia cells in vitro.
AUTHOR: Meng Xue Wei; Chandra Joya; Loegering David; Van Becelaere Keri; Kottke Timothy J; Gore Steven D; Karp Judith E; Sebolt-Leopold Judy; Kaufmann Scott H
CORPORATE SOURCE: Division of Oncology Research, Guggenheim 1342C, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA.
CONTRACT NUMBER: F32 CA 93055 (NCI)
R01 CA 69008 (NCI)
SOURCE: The Journal of biological chemistry, (2003 Nov 21) Vol. 278, No. 47, pp. 47326-39. Electronic Publication: 2003-09-08.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200402
ENTRY DATE: Entered STN: 18 Nov 2003
Last Updated on STN: 4 Feb 2004
Entered Medline: 3 Feb 2004

AB Because the MAPK pathway plays important roles in cell proliferation and inhibition of apoptosis, this pathway has emerged as a potential therapeutic target for solid tumors and leukemia. At the present time there is little information about activation of this pathway and the consequences of its inhibition in acute lymphocytic leukemia cells (ALL). In the present study, constitutive MAPK pathway activation, as evidenced by phosphorylation of ERK1 and ERK2, was observed in 8 of 8 human lymphoid cell lines and 33% (8:24) of pretreatment ALL bone marrows. Inhibition of this pathway by the MEK inhibitors CI-1040 and PD098059 induced apoptosis through a unique pathway involving dephosphorylation and aggregation of Fas-associated death domain protein followed by death receptor-independent caspase-8 activation. Jurkat cell variants lacking Fas-associated death domain protein or procaspase-8 were resistant to CI-1040-induced apoptosis, as were Jurkat or Molt3 cells treated with the O-methyl ester of the caspase-8 inhibitor N-(Nalpha-benzyloxycarbonylisoleucylglutamyl) aspartate fluoromethyl ketone. In contrast, CI-1040-induced apoptosis was unaffected by blocking anti-Fas antibody, soluble tumor necrosis factor-alpha-related apoptosis-inducing ligand decoy receptor,

or transfection with cDNA encoding the anti-apoptotic Bcl-2 family member Mcl-1 or dominant negative caspase-9. Collectively, these results identify the MAPK pathway as a potential therapeutic target in ALL and delineate a mechanism by which MEK inhibition triggers apoptosis in ALL cells.

L10 ANSWER 5 OF 10 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2003246193 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12769332
TITLE: Mitochondria as a target for inducing death of malignant hematopoietic cells.
AUTHOR: Solary Eric; Bettaieb Ali; Dubrez-Daloz Laurence; Corcos Laurent
CORPORATE SOURCE: INSERM U517, IFR 100, 7 boulevard Jeanne d'Arc, 21000 Dijon, France.. esolary@u-bourgogne.fr
SOURCE: Leukemia & lymphoma, (2003 Apr) Vol. 44, No. 4, pp. 563-74. Ref: 144
Journal code: 9007422. ISSN: 1042-8194.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200312
ENTRY DATE: Entered STN: 29 May 2003
Last Updated on STN: 17 Dec 2003
Entered Medline: 5 Dec 2003

AB Mitochondria plays a central role in apoptotic cell death. The intermembrane space of mitochondria contains a number of soluble molecules whose release from the organelle to the cytosol or the nucleus induces cell death. Thus, molecules that directly trigger mitochondria membrane permeabilisation are efficient cytotoxic drugs. Mitochondria is one of the cellular targets for commonly used epipodophyllotoxins, adenine deoxynucleoside analogs and taxanes as well as recently developped agents such as the pentacyclic triterpene betulinic acid and the lymphotoxic agent FTY720. Most informations on anthracyclines point to the mitochondrial membrane as the main target of cardiotoxicity. Mitochondria is also a target for arsenite trioxide, an old cytotoxic agent recently used for treating acute promyelocytic leukemia, lonidamine, a dichlorinated derivative of indazole-3-carboxylic acid developped as a chemosensitizer, the retinoic acid receptor gamma activator CD437 and nitric oxide (NO). Recently, cytotoxic drugs have been specifically designed to directly affect the mitochondrial function. These include the positively charged alpha-helical peptides, which are attracted to and disrupt the negatively charged mitochondrial membrane, thus inducing mammalian cell apoptosis when targeted intracellularly. Various strategies have been proposed also to directly inhibit Bcl-2 and related anti-apoptotic proteins, including antisense oligonucleotides (e.g. Genasense, currently tested in phase III trials), small molecules that mimic the BH3 dimerization domain of these proteins and kinase inhibitors. Ligands of the mitochondrial benzodiazepine receptor such as the isoquinolone carboxamide derivative PK11195 also overcome the membrane-stabilizing effect of Bcl-2, whereas the adenosine nucleotide translocator (ANT) and the mitochondrial DNA are two other potential cellular targets for cytotoxic agents. Potentially, new compounds directly targeting the mitochondria may be useful in treating hematological malignancies. The challenge is now to selectively target these mitochondria permeabilizing agents to malignant cells. This review briefly summarizes the role of the mitochondria in cell death and describes these various strategies for targeting the mitochondria to induce apoptosis.

L10 ANSWER 6 OF 10 MEDLINE on STN

ACCESSION NUMBER: 2003208665 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12729579
TITLE: Mitochondrial membrane permeabilisation by Bax/Bak.
AUTHOR: Degli Esposti Mauro; Dive Caroline
CORPORATE SOURCE: Cancer Research UK Cellular and Molecular Pharmacology Group, School of Biological Sciences, University of Manchester, G38 Stopford Building, Oxford Road, Manchester M134 9PT, UK.
SOURCE: Biochemical and biophysical research communications, (2003 May 9) Vol. 304, No. 3, pp. 455-61. Ref: 75
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200306
ENTRY DATE: Entered STN: 6 May 2003
Last Updated on STN: 17 Jun 2003
Entered Medline: 16 Jun 2003

AB Recent studies on cells derived from mice deficient in both multi-domain pro-apoptotic genes of the Bcl-2 family, Bax and Bak, suggest that one or other of these proteins are required for the release of apoptogens such as cytochrome c from mitochondria. In addition BH-3 only proteins of this family such as Bid are suggested to act as critical death inducing ligands via interactions with pro- and anti-apoptotic Bcl-2 family proteins with Bax or Bak at the mitochondrial surface. Despite this increase in knowledge it remains unclear precisely how Bak and Bax promote outer mitochondrial membrane (OMM) permeabilisation. We suggest that Bax and Bak may not operate in precisely the same manner and evaluate the current models for their function. We also consider the emerging information that lipid-protein interactions may be crucial to the actions of Bax and Bak.

L10 ANSWER 7 OF 10 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:391990 BIOSIS
DOCUMENT NUMBER: PREV200300391990
TITLE: The role of the C-terminal membrane anchor domain of Bcl-XL in heterodimerization of Bcl-XL and Bax.
AUTHOR(S): Jeong, S-Y. [Reprint Author]; Hsu, Y-T.; Lee, Y-J.; Sharpe, J.; 'Suzuki, M.; Youle, R. J.
CORPORATE SOURCE: SNB, NINDS, NIH, 10 Center Drive 10-5D37, Bethesda, MD, 20892-1414, USA
jeongsy@ninds.nih.gov
SOURCE: FASEB Journal, (March 2003) Vol. 17, No. 4-5, pp. Abstract No. 632.15. http://www.fasebj.org/. e-file.
Meeting Info.: FASEB Meeting on Experimental Biology: Translating the Genome. San Diego, CA, USA. April 11-15, 2003. FASEB.
ISSN: 0892-6638 (ISSN print).
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 27 Aug 2003
Last Updated on STN: 27 Aug 2003

AB Interactions among the Bcl-2 family members play fundamental roles in the regulation of apoptosis. The C-terminal hydrophobic tail of the soluble form of Bax occupies a hydrophobic pocket previously shown to mediate dimer formation in Bcl-XL. Consistent with a model that conformational changes occur in Bax to initiate dimer formation, soluble forms of Bax and Bcl-XL dimerize only in the presence of nonionic detergents. We have found that even in the presence of nonionic

detergents Bcl-XL lacking the C-terminal hydrophobic domain fails to heterodimerize with Bax. Surprisingly, opening of the BH3 pocket of Bax by deleting the C-terminal tail allows Bcl-XL binding even in the absence of detergents and truncation of the C-terminal domain of Bcl-XL obviates this dimer formation. Bak/Bcl-XL and Bax/Bcl-2 heterodimerizations show a similar dependence on the C-terminal tail of the anti-apoptotic members of the family, Bcl-XL and Bcl-2. These results indicate that binding of the C-terminal tail of anti-apoptotic members, Bcl-2 and Bcl-XL, into the BH3 binding pocket of pro-apoptotic members, Bax and Bak, mediates heterodimer formation. These results support a new model for how dimers occur and give insight into the design of potentially therapeutic peptides and ligands that may engage the BH3 pocket of Bcl-2 family members.

L10 ANSWER 8 OF 10 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2002181158 EMBASE
TITLE: Novel triterpenoid CDDO-Me is a potent inducer of apoptosis and differentiation in acute myelogenous leukemia.
AUTHOR: Konopleva M.; Tsao T.; Ruvolo P.; Stiouf I.; Estrov Z.; Leysath C.E.; Zhao S.; Harris D.; Chang S.; Jackson C.E.; Munsell M.; Suh N.; Gribble G.; Honda T.; May W.S.; Sporn M.B.; Andreeff M.
CORPORATE SOURCE: M. Andreeff, Dept. Blood/Marrow Transplantation, Section of Molecular Hematology, Univ. TX M.D. Anderson Cancer Ctr., 1515 Holcombe Blvd, Houston, TX 77030, United States. mandreef@mdanderson.org
SOURCE: Blood, (1 Jan 2002) Vol. 99, No. 1, pp. 326-335.
Refs: 73
ISSN: 0006-4971 CODEN: BLOOAW
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
025 Hematology
037 Drug Literature Index
006 Internal Medicine
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 6 Jun 2002
Last Updated on STN: 6 Jun 2002

AB It has been shown that the novel synthetic triterpenoid CDDO inhibits proliferation and induces differentiation and apoptosis in myeloid leukemia cells. In the current study the effects of the C-28 methyl ester of CDDO, CDDO-Me, were analyzed on cell growth and apoptosis of leukemic cell lines and primary acute myelogenous leukemia (AML). CDDO-Me decreased the viability of leukemic cell lines, including multidrug resistant (MDR)-1-overexpressing, p53(null) HL-60-Dox and of primary AML cells, and it was 3- to 5-fold more active than CDDO. CDDO-Me induced a loss of mitochondrial membrane potential, induction of caspase-3 cleavage, increase in annexin V binding and DNA fragmentation, suggesting the induction of apoptosis. CDDO-Me induced proapoptotic Bax protein that preceded caspase activation. Furthermore, CDDO-Me inhibited the activation of ERK1/2, as determined by the inhibition of mitochondrial ERK1/2 phosphorylation, and it blocked Bcl-2 phosphorylation, rendering Bcl-2 less anti-apoptotic. CDDO-Me induced granulo-monocytic differentiation in HL-60 cells and monocytic differentiation in primary cells. Of significance, colony formation of AML progenitors was significantly inhibited in a dose-dependent fashion, whereas normal CD34(+) progenitor cells were less affected. Combinations with ATRA or the RXR-specific ligand LG100268 enhanced the effects of CDDO-Me on cell viability

and terminal differentiation of myeloid leukemic cell lines. In conclusion, CDDO-Me is an MDR-1- and a p53-independent compound that exerts strong antiproliferative, apoptotic, and differentiating effects in myeloid leukemic cell lines and in primary AML samples when given in submicromolar concentrations. Differential effects of CDDO-Me on leukemic and normal progenitor cells suggest that CDDO-Me has potential as a novel compound in the treatment of hematologic malignancies. .COPYRGT. 2002 by The American Society of Hematology.

L10 ANSWER 9 OF 10 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2000302778 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10843681
TITLE: The ADP-ribosylating CTA1-DD adjuvant enhances T cell-dependent and independent responses by direct action on B cells involving anti-apoptotic Bcl-2- and germinal center-promoting effects.
AUTHOR: Agren L; Sverremark E; Ekman L; Schon K; Lowenadler B; Fernandez C; Lycke N
CORPORATE SOURCE: Department of Medical Microbiology and Immunology, University of Goteborg, Sweden.
CONTRACT NUMBER: R01AI40701 (NIAID)
SOURCE: Journal of immunology (Baltimore, Md. : 1950), (2000 Jun 15) Vol. 164, No. 12, pp. 6276-86.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: (COMPARATIVE STUDY)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200007
ENTRY DATE: Entered STN: 28 Jul 2000
Last Updated on STN: 28 Jul 2000
Entered Medline: 20 Jul 2000

AB We recently developed a novel immunomodulating gene fusion protein, CTA1-DD, that combines the ADP-ribosylating ability of cholera toxin (CT) with a dimer of an Ig-binding fragment, D, of Staphylococcus aureus protein A. The CTA1-DD adjuvant was found to be nontoxic and greatly augmented T cell-dependent responses to soluble protein Ags after systemic as well as mucosal immunizations. Here we show that CTA1-DD does not appear to form immune complexes or bind to soluble Ig following injections, but, rather, it binds directly to B cells of all isotypes, including naive IgD+ cells. No binding was observed to macrophages or dendritic cells. Immunizations in FcepsilonR (common FcRgamma-chain)- and FcgammaRII-deficient mice demonstrated that CTA1-DD exerted unaltered enhancing effects, indicating that FcgammaR-expressing cells are not required for the adjuvant function. Whereas CT failed to augment Ab responses to high m.w. dextran B512 in athymic mice, CTA1-DD was highly efficient, demonstrating that T cell-independent responses were also enhanced by this adjuvant. In normal mice both CT and CTA1-DD, but not the enzymatically inactive CTA1-R7K-DD mutant, were efficient enhancers of T cell-dependent as well as T cell-independent responses, and both promoted germinal center formation following immunizations. Although CT augmented apoptosis in Ag receptor-activated B cells, CTA1-DD strongly counteracted apoptosis by inducing Bcl-2 in a dose-dependent manner, a mechanism that was independent of the CD19 coreceptor. However, in the presence of CD40 stimulation, apoptosis was low and unaffected by CT, suggesting that the adjuvant effect of CT is dependent on the presence of activated CD40 ligand-expressing T cells.

L10 ANSWER 10 OF 10 MEDLINE on STN DUPLICATE 5

ACCESSION NUMBER: 97450918 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9305851
TITLE: BH3 domain of BAD is required for heterodimerization with BCL-XL and pro-apoptotic activity.
AUTHOR: Zha J; Harada H; Osipov K; Jockel J; Waksman G; Korsmeyer S J
CORPORATE SOURCE: Howard Hughes Medical Institute, Department of Medicine and Pathology, Washington University School of Medicine, St. Louis, Missouri 63110, USA.
SOURCE: The Journal of biological chemistry, (1997 Sep 26) Vol. 272, No. 39, pp. 24101-4.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199710
ENTRY DATE: Entered STN: 5 Nov 1997
Last Updated on STN: 5 Nov 1997
Entered Medline: 23 Oct 1997

AB BAD interacts with anti-apoptotic molecules BCL-2 and BCL-XL and promotes apoptosis. BAD is phosphorylated on serine residues in response to a survival factor, interleukin-3. Phosphorylated BAD cannot bind to BCL-XL or BCL-2 at membrane sites and is found in the cytosol bound to 14-3-3. We report here that deletion mapping and site-directed mutagenesis identified a BH3 domain within BAD that proved necessary for both its heterodimerization with BCL-XL and its death agonist activity. Substitution of the conserved Leu151 with Ala in the BH3 amphipathic alpha-helix abrogated both functions. The BAD Leu151 mutant was predominantly in the cytosol bound to 14-3-3. The BH3 domain of BCL-2 also proved important for BCL-2/BAD interaction. These results establish a critical role for a BH3 domain within BAD and provide evidence that BAD may function as a death ligand whose pro-apoptotic activity requires heterodimerization with BCL-XL.

=> d his

(FILE 'HOME' ENTERED AT 10:14:24 ON 05 NOV 2007)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 10:14:54 ON 05 NOV 2007

L1 134033 S "BCL-2"
L2 36036 S ANTI(W)APOPTOTIC
L3 14816 S L1 AND L2
L4 155793 S "BCL###"
L5 14816 S L3 AND L4
L6 141558 S "BCL-XL" OR "BCL-2" OR "BCL-W"
L7 14816 S L5 AND L6
L8 245 S DIMER? AND L7
L9 25 S LIGAND? AND L8
L10 10 DUP REM L9 (15 DUPLICATES REMOVED)

=> e geneste o/au
E1 7 GENESTE M/AU
E2 2 GENESTE M B/AU
E3 77 --> GENESTE O/AU
E4 1 GENESTE OLIVER/AU
E5 54 GENESTE OLIVIER/AU
E6 284 GENESTE P/AU
E7 1 GENESTE PATRIC/AU
E8 142 GENESTE PATRICK/AU

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E9          45      GENESTE R/AU
E10          1      GENESTE RICHARD/AU
E11          1      GENESTE THIERRY/AU
E12          2      GENESTER C/AU

=> s e5
L11         54 "GENESTE OLIVIER"/AU

=> e hickman j/au
E1          23      HICKMAN INGRID J/AU
E2           2      HICKMAN IOLA/AU
E3         264 --> HICKMAN J/AU
E4           1      HICKMAN J 0/AU
E5         801      HICKMAN J A/AU
E6           3      HICKMAN J A */AU
E7          13      HICKMAN J B/AU
E8          34      HICKMAN J C/AU
E9          11      HICKMAN J E/AU
E10         13      HICKMAN J F/AU
E11         49      HICKMAN J G/AU
E12          3      HICKMAN J H/AU

=> s e3
L12        264 "HICKMAN J"/AU

=> e bennett r/au
E1           1      BENNETT Q/AU
E2           2      BENNETT Q M/AU
E3         999 --> BENNETT R/AU
E4         475      BENNETT R A/AU
E5          63      BENNETT R A O/AU
E6           5      BENNETT R ALAN/AU
E7          37      BENNETT R AVERY/AU
E8         100      BENNETT R B/AU
E9           4      BENNETT R B III/AU
E10        396      BENNETT R C/AU
E11        214      BENNETT R D/AU
E12          1      BENNETT R DOUGLAS/AU

=> s e3
L13        999 "BENNETT R"/AU

=> e rain j c/au
E1           1      RAIN H/AU
E2          17      RAIN J/AU
E3          87 --> RAIN J C/AU
E4         492      RAIN J D/AU
E5           1      RAIN J F/AU
E6           4      RAIN J J/AU
E7           2      RAIN J S/AU
E8           1      RAIN JC/AU
E9          75      RAIN JEAN CHRISTOPHE/AU
E10          3      RAIN JEAN D/AU
E11          1      RAIN JEAN DIDER/AU
E12         70      RAIN JEAN DIDIER/AU

=> s e3
L14         87 "RAIN J C"/AU

=> d his

     (FILE 'HOME' ENTERED AT 10:14:24 ON 05 NOV 2007)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
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     LIFESCI' ENTERED AT 10:14:54 ON 05 NOV 2007
L1        134033 S "BCL-2"
L2         36036 S ANTI(W)APOPTOTIC
L3         14816 S L1 AND L2
L4        155793 S "BCL###"
L5         14816 S L3 AND L4
L6        141558 S "BCL-XL" OR "BCL-2" OR "BCL-W"
L7         14816 S L5 AND L6
L8           245 S DIMER? AND L7
L9            25 S LIGAND? AND L8
L10           10 DUP REM L9 (15 DUPLICATES REMOVED)
                 E GENESTE O/AU
L11           54 S E5
                 E HICKMAN J/AU
L12          264 S E3
                 E BENNETT R/AU
L13          999 S E3
                 E RAIN J C/AU
L14           87 S E3

=> s l11 or l12 or l13 or l14
L15        1399 L11 OR L12 OR L13 OR L14

=> s l8 and l15
L16           0 L8 AND L15

=> s l1 and l`15
<------User Break------>

SEARCH ENDED BY USER

=> s l1 and l15
L17           25 L1 AND L15

=> dup rem l17
PROCESSING COMPLETED FOR L17
L18           10 DUP REM L17 (15 DUPLICATES REMOVED)

=> d 1-10 ibib ab

L18  ANSWER 1 OF 10      MEDLINE on STN
ACCESSION NUMBER:    2007324164      MEDLINE
DOCUMENT NUMBER:     PubMed ID: 17438366
TITLE:               BH3-only proteins and BH3 mimetics induce autophagy by
                     competitively disrupting the interaction between Beclin 1
                     and Bcl-2/Bcl-X(L).
AUTHOR:              Maiuri Maria Chiara; Criollo Alfredo; Tasdemir Ezgi;
                     Vicencio Jose Miguel; Tajeddine Nicolas; Hickman John A;
                     Geneste Olivier; Kroemer Guido
CORPORATE SOURCE:    INSERM, U848, Villejuif, France.
SOURCE:              Autophagy, (2007 Jul-Aug) Vol. 3, No. 4, pp. 374-6.
                     Electronic Publication: 2007-07-04.
                     Journal code: 101265188. ISSN: 1554-8627.
PUB. COUNTRY:        United States
DOCUMENT TYPE:       Commentary
                     Journal; Article; (JOURNAL ARTICLE)
                     (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE:            English
FILE SEGMENT:        Priority Journals
ENTRY MONTH:         200708
ENTRY DATE:          Entered STN: 1 Jun 2007
                     Last Updated on STN: 31 Aug 2007
                     Entered Medline: 30 Aug 2007
AB   Beclin 1 has recently been identified as novel BH3-only protein, meaning
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that it carries one Bcl-2-homology-3 (BH3) domain. As other BH3-only proteins, Beclin 1 interacts with anti-apoptotic multidomain proteins of the Bcl-2 family (in particular Bcl-2 and its homologue Bcl-X(L)) by virtue of its BH3 domain, an amphipathic alpha-helix that binds to the hydrophobic cleft of Bcl-2/Bcl-X(L). The BH3 domains of other BH3-only proteins such as Bad, as well as BH3-mimetic compounds such as ABT737, competitively disrupt the inhibitory interaction between Beclin 1 and Bcl-2/Bcl-X(L). This causes autophagy of mitochondria (mitophagy) but not of the endoplasmic reticulum (reticulophagy). Only ER-targeted (not mitochondrion-targeted) Bcl-2/Bcl-X(L) can inhibit autophagy induced by Beclin 1, and only Beclin 1-Bcl-2/Bcl-X(L) complexes present in the ER (but not those present on heavy membrane fractions enriched in mitochondria) are disrupted by ABT737. These findings suggest that the Beclin 1-Bcl-2/Bcl-X(L) complexes that normally inhibit autophagy are specifically located in the ER and point to an organelle-specific regulation of autophagy. Furthermore, these data suggest a spatial organization of autophagy and apoptosis control in which BH3-only proteins exert two independent functions. On the one hand, they can induce apoptosis, by (directly or indirectly) activating the mitochondrion-permeabilizing function of pro-apoptotic multidomain proteins from the Bcl-2 family. On the other hand, they can activate autophagy by liberating Beclin 1 from its inhibition by Bcl-2/Bcl-X(L) at the level of the endoplasmic reticulum.

L18 ANSWER 2 OF 10 MEDLINE on STN DUPLICATE 1

ACCESSION NUMBER: 2007341822 MEDLINE
DOCUMENT NUMBER: PubMed ID: 17446862
TITLE: Functional and physical interaction between Bcl-X(L) and a BH3-like domain in Beclin-1.
AUTHOR: Maiuri M Chiara; Le Toumelin Gaetane; Criollo Alfredo; Rain Jean-Christophe; Gautier Fabien; Juin Philippe; Tasdemir Ezgi; Pierron Gerard; Troulinaki Kostoula; Tavernarakis Nektarios; Hickman John A; Geneste Olivier; Kroemer Guido
CORPORATE SOURCE: INSERM U848, Villejuif, France.
SOURCE: The EMBO journal, (2007 May 16) Vol. 26, No. 10, pp. 2527-39. Electronic Publication: 2007-04-19. Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200706
ENTRY DATE: Entered STN: 9 Jun 2007
Last Updated on STN: 30 Jun 2007
Entered Medline: 29 Jun 2007

AB The anti-apoptotic proteins Bcl-2 and Bcl-X(L) bind and inhibit Beclin-1, an essential mediator of autophagy. Here, we demonstrate that this interaction involves a BH3 domain within Beclin-1 (residues 114-123). The physical interaction between Beclin-1 and Bcl-X(L) is lost when the BH3 domain of Beclin-1 or the BH3 receptor domain of Bcl-X(L) is mutated. Mutation of the BH3 domain of Beclin-1 or of the BH3 receptor domain of Bcl-X(L) abolishes the Bcl-X(L)-mediated inhibition of autophagy triggered by Beclin-1. The pharmacological BH3 mimetic ABT737 competitively inhibits the interaction between Beclin-1 and Bcl-2/Bcl-X(L), antagonizes autophagy inhibition by Bcl-2/Bcl-X(L) and hence stimulates autophagy. Knockout or knockdown of the BH3-only protein Bad reduces starvation-induced autophagy, whereas Bad overexpression induces autophagy in human cells. Gain-of-function mutation of the sole BH3-only protein from Caenorhabditis

elegans, EGL-1, induces autophagy, while deletion of EGL-1 compromises starvation-induced autophagy. These results reveal a novel autophagy-stimulatory function of BH3-only proteins beyond their established role as apoptosis inducers. BH3-only proteins and pharmacological BH3 mimetics induce autophagy by competitively disrupting the interaction between Beclin-1 and Bcl-2 or Bcl-X(L).

L18 ANSWER 3 OF 10 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
DUPLICATE 2
ACCESSION NUMBER: 2007:469333 BIOSIS
DOCUMENT NUMBER: PREV200700466164
TITLE: BH3-only proteins and BH3 mimetics induce autophagy by competitively disrupting the interaction between Beclin 1 and Bcl-2/Bcl-X-L.
AUTHOR(S): Maiuri, Maria Chiara; Criollo, Alfredo; Tasdemir, Ezgi; Vicencio, Jose Miguel; Tajeddine, Nicolas; Hickman, John A.; Geneste, Olivier; Kroemer, Guido [Reprint Author]
CORPORATE SOURCE: Inst Gustave Roussy, INSERM, U848, PRI, 39 Rue Camille Desmoulins, F-94805 Villejuif, France kroemer@igr.fr
SOURCE: Autophagy, (JUL-AUG 2007) Vol. 3, No. 4, pp. 374-376. ISSN: 1554-8627. E-ISSN: 1554-8635.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 5 Sep 2007
Last Updated on STN: 5 Sep 2007
AB Beclin 1 has recently been identified as novel BH3-only protein, meaning that it carries one Bcl-2-homology-3 (BH3) domain. As other BH3-only proteins, Beclin 1 interacts with anti-apoptotic multidomain proteins of the Bcl-2 family (in particular Bcl-2 and its homologue Bcl-X-L) by virtue of its BH3 domain, an amphipathic a-helix that binds to the hydrophobic cleft of Bcl-2/Bcl-X-L. The BH3 domains of other BH3-only proteins such as Bad, as well as BH3-mimetic compounds such as ABT737, competitively disrupt the inhibitory interaction between Beclin 1 and Bcl-2/Bcl-X-L. This causes autophagy of mitochondria (mitophagy) but not of the endoplasmic reticulum (reticulophagy). Only ER-targeted (not mitochondrion-targeted) Bcl-2/Bcl-X-L can inhibit autophagy induced by Beclin 1, and only Beclin 1-Bcl-2/Bcl-X-L complexes present in the ER (but not those present on heavy membrane fractions enriched in mitochondria) are disrupted by ABT737. These findings suggest that the Beclin 1-Bcl-2/Bcl-X-L complexes that normally inhibit autophagy are specifically located in the ER and point to an organelle-specific regulation of autophagy. Furthermore, these data suggest a spatial organization of autophagy and apoptosis control in which BH3-only proteins exert two independent functions. On the one hand, they can induce apoptosis, by (directly or indirectly) activating the mitochondrion-permeabilizing function of pro-apoptotic multidomain proteins from the Bcl-2 family. On the other hand, they can activate autophagy by liberating Beclin 1 from its inhibition by Bcl-2/Bcl-X-L at the level of the endoplasmic reticulum.

L18 ANSWER 4 OF 10 BIOTECHDS COPYRIGHT 2007 THE THOMSON CORP. on STN
DUPLICATE 3
ACCESSION NUMBER: 2006-21503 BIOTECHDS
TITLE: Peptide interacting with anti-apoptotic members of Bcl-2 protein family useful for the treatment of cancers,;
protein interaction and recombinant vector expression in host cell for disease therapy
AUTHOR: GENESTE O; HICKMAN J; RAIN J C

PATENT ASSIGNEE: LES LAB SERVIER SA; HYBRIGENICS
PATENT INFO: FR 2881430 4 Aug 2006
APPLICATION INFO: FR 2005-978 1 Feb 2005
PRIORITY INFO: FR 2005-978 1 Feb 2005; FR 2005-978 1 Feb 2005
DOCUMENT TYPE: Patent
LANGUAGE: French
OTHER SOURCE: WPI: 2006-571572 [59]
AB DERWENT ABSTRACT:
NOVELTY - A peptide interacting with members of the anti-apoptotic Bcl-2 protein family comprising a fully defined 24 amino acid sequence (SEQ ID NO. 1-6) given in the specification, or their functional variants, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for: (1) nucleic acid sequences encoding the peptide; (2) a recombinant vector comprising the nucleic acid sequence; (3) a host cell comprising the vector; (4) a pharmaceutical composition comprising the peptide; and (5) identifying (M1) modulators of the interaction of the peptide and an anti-apoptotic Bcl-2 family member comprising: (a) contacting the peptide with an anti-apoptotic Bcl-2 family member; (b) adding the test compound; and (c) measuring the activity of the test compound which modulates interaction between the peptide and anti-apoptotic Bcl-2 family member and comparing it to a measurment taken in the absence of the test compound.

BIOTECHNOLOGY - Preferred Nucleic Acid Sequence: The nucleic acids comprise (SEQ ID NO. 7-11) fully defined in the specification. Preferred Vector: The vector is a plasmid, cosmid, artificial bacterial chromosome or a bacteriophage comprising the sequences necessary for the expression of the peptide, under the control of a promoter of transcription and/or transduction. Preferred Host Cell: The host cell is a bacteria or a eukaryotic cell. Preferred Method: (M1) also comprises: (a) marking the peptide with a fluorescent marker; (b) incubating the peptide in the presence of the test compound; (c) adding the anti-apoptotic Bcl -2 family member; (d) measuring the polarisation of fluorescence; and (e) comparing the measurement with and without the test compound. The modulator increases or diminishes the amount of polarization of fluorescence. The fluorescent probe is fluorescein. The anti-apoptotic Bcl-2 family member is particularly Bcl-2, Bcl-XL or Bcl-W.

ACTIVITY - Cytostatic; Apoptotic. No biological data given.

MECHANISM OF ACTION - None given.

USE - The peptide is useful in a pharmaceutical composition used for treating cancer by inducing programmed cell death (claimed).(41 pages)

L18 ANSWER 5 OF 10 BIOTECHDS COPYRIGHT 2007 THE THOMSON CORP. on STN
DUPLICATE 4
ACCESSION NUMBER: 2006-21502 BIOTECHDS
TITLE: Identifying modulators of programmed cell death, useful for treating cancer, comprising interacting the motif of beclin protein and anti-apoptotic member of the Bcl-2, Bcl-XL/Bcl-W protein family; programmed cell death modulator identification and vector expression host cell for use in disease therapy
AUTHOR: GENESTE O; HICKMAN J; RAIN J C
PATENT ASSIGNEE: LES LAB SERVIER SA; HYBRIGENICS
PATENT INFO: FR 2881429 4 Aug 2006
APPLICATION INFO: FR 2005-977 1 Feb 2005
PRIORITY INFO: FR 2005-977 1 Feb 2005; FR 2005-977 1 Feb 2005
DOCUMENT TYPE: Patent
LANGUAGE: French
OTHER SOURCE: WPI: 2006-571571 [59]
AB DERWENT ABSTRACT:
NOVELTY - Identifying modulators of programmed cell death, comprising interacting the motif of beclin protein and anti-apoptotic member of Bcl-2, Bcl-XL/Bcl-W protein family and detecting the

interaction optionally in presence of a compound to be tested, is new.

DETAILED DESCRIPTION - Identifying modulators of programmed dead cells, comprising interacting the motif of beclin protein and anti-apoptotic member of Bcl-2, Bcl-XL/Bcl-W protein family and detecting the interaction optionally in presence of a compound, is new. The motif comprises Gly-Thr-Met-Glu-Asn-Leu-Ser-Arg-Arg-Leu-Lys-Val-Thr-Gly-Asp-Leu-Phe-Asp-Ile-Met-Ser-Gly-Gln-Thr-Asp-Val (SEQ ID NO. 1). INDEPENDENT CLAIMS are included for: (1) a sequence of amino acids comprising (SEQ ID NO. 1); (2) a nucleic acid sequence (SEQ ID NO. 2) encoding the amino acid sequence of (1); (3) a nucleic acid sequence deduced from the genetic code of (SEQ ID NO. 1); (4) a recombinant vector comprising the nucleic acid sequence of (2);(5) a host cell transformed by the vector of (5); (6) a peptide comprising (SEQ ID NO. 1); (7) a peptide encoded by (SEQ ID NO. 2) or the nucleic acid sequence of (3); (5) a pharmaceutical composition comprising the peptide of (6) or (7).

BIOTECHNOLOGY - Preferred Method: The method further comprises marking the motif by fluorescein; adding an anti-apoptotic member to the motif; incubating the system; measuring of the fluorescence polarization; and comparing the measurement with or without the compound to be tested. The interaction is an inhibitor decreasing or an activator increasing the fluorescence polarizations. The anti-apoptotic member is a member of the Bcl-2 family of proteins, particularly Bcl-2, Bcl-XL or Bcl-W. Preferred Vector: The vector is a plasmid, a cosmid, an artificial bacterial chomosome or a bacteriophage comprising the sequences necessary for the expression of the Beclin protein motif, including a promoter sequence of transcription and transduction.

ACTIVITY - Cytostatic; Apoptotic. No biological data given.

MECHANISM OF ACTION - None given.

USE - The pharmaceutical composition is useful as an inductor of apoptotic and/or autophagic cell death for treating cancer (claimed).(35 pages)

L18 ANSWER 6 OF 10 MEDLINE on STN DUPLICATE 5

ACCESSION NUMBER: 2006123527 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16510597
TITLE: The small organic compound HA14-1 prevents Bcl-2 interaction with Bax to sensitize malignant glioma cells to induction of cell death.
AUTHOR: Manero Florence; Gautier Fabien; Gallenne Tristan; Cauquil Nicolas; Gree Danielle; Cartron Pierre-Francois; Geneste Olivier; Gree Rene; Vallette Francois M; Juin Philippe
CORPORATE SOURCE: Institut National de la Sante et de la Reserche Medicale U601, Departement de Recherche en Cancerologie, Nantes, France.
SOURCE: Cancer research, (2006 Mar 1) Vol. 66, No. 5, pp. 2757-64. Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200604
ENTRY DATE: Entered STN: 3 Mar 2006
Last Updated on STN: 19 Apr 2006
Entered Medline: 18 Apr 2006

AB A functional imbalance between proapoptotic Bax and antiapoptotic Bcl-2 is likely to participate in the resistance of cancer cells to therapy. We show here that ethyl 2-amino-6-bromo-4-(1-cyano-2-ethoxy-2-oxoethyl)-4H-chromene-3-carboxylate (HA14-1), a small organic compound recently proposed to function as an inhibitor of Bcl-2, increases the sensitivity of human glioblastoma cells to radiotherapy and chemotherapy. This sensitizing effect is lost if Bcl-2 expression, but not Bcl-xL expression, is

knocked down or if cells only express a mutant of Bax that does not interact with Bcl-2. This points to a specific Bcl-2 inhibitory function of HA14-1 and implies that it selectively involves hindrance of Bcl-2 binding to Bax, which HA14-1 inhibits in cell-free assays and in cells in receipt of an apoptotic stimulation. Moreover, HA14-1, in combination with a cytotoxic treatment, slows down the growth of glioblastoma in vivo. Thus, the inhibition of Bcl-2 achieved by HA14-1 might improve treatment outcome.

L18 ANSWER 7 OF 10 BIOTECHDS COPYRIGHT 2007 THE THOMSON CORP. on STN
DUPLICATE 6
ACCESSION NUMBER: 2005-09128 BIOTECHDS
TITLE: New peptide that binds Bcl-2 and Bcl-XL, useful in screening for modulators of apoptosis, potentially useful for treating e.g., autoimmune diseases and cancer; recombinant protein production via plasmid expression in host cell for use in disease therapy
AUTHOR: GENESTE O; HICKMAN J; BENNETT R; RAIN J C
PATENT ASSIGNEE: LES LAB SERVIER SA; HYBRIGENICS
PATENT INFO: FR 2858621 11 Feb 2005
APPLICATION INFO: FR 2003-9697 6 Aug 2003
PRIORITY INFO: FR 2003-9697 6 Aug 2003; FR 2003-9697 6 Aug 2003
DOCUMENT TYPE: Patent
LANGUAGE: French
OTHER SOURCE: WPI: 2005-155005 [17]
AB DERWENT ABSTRACT:
NOVELTY - A peptide (I) that interacts with the antiapoptotic proteins Bcl-2 and/or Bcl-XL, is new.

DETAILED DESCRIPTION - A peptide (I) that interacts with the antiapoptotic proteins Bcl-2 and/or Bcl-XL, is new.
INDEPENDENT CLAIMS are also included for: (1) a peptide (Ia) that is a fragment or point mutant of (I); (2) a nucleic acid sequence (II) encoding (I); 5'-GATACCCGTCGCAGCATGGTGTTTGCCAGGCACCTGCGGGAGGTGGGAGACGAGTT CAGGAGCAGA-3' (2); (3) a deduced nucleic acid sequence (IIa) for (I) and (Ia); (4) a recombinant (expression) vector that contains (II) or (IIa); (5) a host cell transformed by the vector of (4); and (6) identifying molecules (III) that modulate the interaction between (I) or (Ia) and an antiapoptotic protein. Asp-Thr-Arg-Arg-Ser-Met-Val-Phe-Ala-Arg-His-Leu-Arg-Glu-Val-Gly-Asp-Glu-Phe-Arg-Ser-Arg (I); 5'-GATACCCGTCGCAGCATGGTGTTTGCCAGGCACCTGCGGGAGGTGGGAGACGAGTTCAGGAGCAGA-3' (II);

BIOTECHNOLOGY - Preferred Process: In identifying molecules that modulate the interaction between (I) or (Ia) and an antiapoptotic protein a fluorescently labeled (I) or (Ia) is incubated with a test compound, a fusion protein containing the antiapoptotic protein is added and fluorescence polarization is measured. Compounds that reduce the fluorescence polarization are inhibitors of the interaction and compounds which increase fluorescence polarization are promoters of the interaction. Preferred labels are Oregon Green, bodipy and fluorescein (most preferred). Isolation: (I) was identified in a two hybrid assay, using Bcl-2/-XL as the bait and human cDNA banks as prey. Its ability to induce apoptosis was confirmed by transformation/microinjection of cells.

ACTIVITY - Cytostatic; Immunosuppressive; Neuroprotective; Apoptotic; Antiapoptotic.

MECHANISM OF ACTION - Bcl-2 modulator; Bcl-XL modulator; Apoptosis modulator.

USE - (I), and its fragments and point mutants, are used to identify molecules that modulate apoptosis and/or are useful in treating diseases that involve deregulation of apoptosis, particularly autoimmune diseases, some (degenerative) neurological diseases and cancer (claimed).

ADVANTAGE - Since (I) is a small peptide, it is ideally suited for

high efficiency screening for modulators of protein interactions. (23 pages)

L18 ANSWER 8 OF 10 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 2006084707 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16471266
TITLE: [The Bcl-2 family of proteins as drug targets].
Antagonistes de Bcl-2, therapies anticancereuses alternatives.
AUTHOR: Mazars Anne; Geneste Olivier; Hickman John
CORPORATE SOURCE: Institut de Recherches Servier, Division Recherche Cancerologie, 125, Chemin de Ronde, 78290 Croissy/Seine, France.. anne.mazars@fr.netgrs.com
SOURCE: Journal de la Societe de biologie, (2005) Vol. 199, No. 3, pp. 253-65. Ref: 117
Journal code: 100890617. ISSN: 1295-0661.
PUB. COUNTRY: France
DOCUMENT TYPE: (ENGLISH ABSTRACT)
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: French
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200603
ENTRY DATE: Entered STN: 14 Feb 2006
Last Updated on STN: 25 Mar 2006
Entered Medline: 24 Mar 2006

AB Programmed cell death or apoptosis is a crucial process for normal embryonic development and homeostasis. Apoptosis is known to be coupled to multiple signalling pathways. Identification of critical points in the regulation of apoptosis is of major interest both for the understanding of control of cell fate and for the discovery of new pharmacological targets, particularly in oncology. Indeed, defects in the execution of apoptosis are known to participate in tumour initiation and progression as well as in chemoresistance. The Bcl-2 family members constitute essential intracellular players in the apoptotic machinery. Those proteins are either pro or anti-apoptotic, they interact with each other to regulate apoptosis. Inhibiting the heterodimerisation between pro- and anti-apoptotic members is sufficient to promote apoptosis in mammalian cells. Small molecules, antagonists or peptidomimetics inhibiting this heterodimerisation, represent a therapeutic prototype targeting the apoptotic cascade. They induce cell death by activating directly the mitochondrial apoptotic pathway. Considerable evidence indicate that such Bcl-2 antagonists could be useful drugs to induce apoptosis preferentially in neoplastic cells.

L18 ANSWER 9 OF 10 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 2004105224 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14996507
TITLE: Shooting at survivors: Bcl-2 family members as drug targets for cancer.
AUTHOR: Juin Philippe; Geneste Olivier; Raimbaud Eric; Hickman John A
CORPORATE SOURCE: Univ. de Nantes, INSERM U419, 44035 Nantes Cedex 035, France.. pjuin@nantes.inserm.fr
SOURCE: Biochimica et biophysica acta, (2004 Mar 1) Vol. 1644, No. 2-3, pp. 251-60. Ref: 82
Journal code: 0217513. ISSN: 0006-3002.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200404

ENTRY DATE: Entered STN: 4 Mar 2004
Last Updated on STN: 27 Apr 2004
Entered Medline: 26 Apr 2004

L18 ANSWER 10 OF 10 SCISEARCH COPYRIGHT (c) 2007 The Thomson Corporation on STN
ACCESSION NUMBER: 1994:220230 SCISEARCH
THE GENUINE ARTICLE: NE758
TITLE: CHARACTERIZATION OF RADIATION-INDUCED APOPTOSIS IN THE SMALL-INTESTINE AND ITS BIOLOGICAL IMPLICATIONS
AUTHOR: POTTEN C S (Reprint); MERRITT A; HICKMAN J; HALL P; FARANDA A
CORPORATE SOURCE: CHRISTIE HOSP & HOLT RADIUM INST, PATERSON INST CANC RES, CRC, DEPT EPITHELIAL BIOL, WILMSLOW RD, MANCHESTER M20 9BX, LANCS, ENGLAND (Reprint); UNIV MANCHESTER, SCH BIOL SCI, CRC, MOLEC & CELLULAR PHARMACOL GRP, MANCHESTER M13 9PT, LANCS, ENGLAND; ST THOMAS HOSP, DEPT HISTOPATHOL, LONDON SE1 7EH, ENGLAND
COUNTRY OF AUTHOR: ENGLAND
SOURCE: INTERNATIONAL JOURNAL OF RADIATION BIOLOGY, (JAN 1994) Vol. 65, No. 1, pp. 71-78.
ISSN: 0955-3002.
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ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The small intestine with its high cell proliferation, well-accepted hierarchy, high radiation susceptibility and low cancer incidence is a useful model for studying the controls of cell replacement. Apoptosis, which represents part of the overall homeostatic process, occurs spontaneously at the stem cell position in the crypts, and very small doses of radiation elevate the levels of apoptosis rapidly in this region. Other cytotoxic agents also target cells in this region including several mutagenic chemicals. Yet other drugs target cells at higher positions in the crypt indicating that all crypt cells possess the programme for apoptosis, but this is normally suppressed in many of the cells. In contrast, high doses of radiation are required to reproductively sterilize the crypts and, using clonal regeneration techniques, the number of clonogenic cells is dependent on the levels of damage induced (dose), i.e. the more injury that is induced the greater number of cells that are recruited into the clonogenic compartment. All doses of radiation trigger rapid changes in proliferation in the stem cell region which suggests that the detection of the induced cell death (even small levels, such as one apoptotic cell per crypt) is efficient and has rapid consequences, p53 may be involved in this damage recognition and apoptosis initiation. The studies to date suggest that apoptosis plays an important role in this tissue in terms of its homeostasis and its protection against carcinogenesis by removal of potentially carcinogenic damaged cells.

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(FILE 'HOME' ENTERED AT 10:14:24 ON 05 NOV 2007)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 10:14:54 ON 05 NOV 2007
L1 134033 S "BCL-2"
L2 36036 S ANTI(W)APOPTOTIC
L3 14816 S L1 AND L2

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L4        155793 S "BCL###"
L5         14816 S L3 AND L4
L6        141558 S "BCL-XL" OR "BCL-2" OR "BCL-W"
L7         14816 S L5 AND L6
L8           245 S DIMER? AND L7
L9            25 S LIGAND? AND L8
L10           10 DUP REM L9 (15 DUPLICATES REMOVED)
                 E GENESTE O/AU
L11           54 S E5
                 E HICKMAN J/AU
L12          264 S E3
                 E BENNETT R/AU
L13          999 S E3
                 E RAIN J C/AU
L14           87 S E3
L15         1399 S L11 OR L12 OR L13 OR L14
L16            0 S L8 AND L15
L17           25 S L1 AND L15
L18           10 DUP REM L17 (15 DUPLICATES REMOVED)
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	Document ID	Kind Codes	Source	Issue Date	Pages
1	US 20060183688 A1		US-PGPUB	20060817	10
2	US 20050244844 A1		US-PGPUB	20051103	48
3	US 20040253629 A1		US-PGPUB	20041216	26
4	US 20030216427 A1		US-PGPUB	20031120	99
5	US 20020076794 A1		US-PGPUB	20020620	20
6	US 7018988 B2		USPAT	20060328	74
7	US 6780604 B2		USPAT	20040824	25
8	US 6770656 B2		USPAT	20040803	87
9	US 6437097 B1		USPAT	20020820	26
10	US 6376247 B1		USPAT	20020423	25
11	US 6222017 B1		USPAT	20010424	25
12	US 6043055 A		USPAT	20000328	25

	Title
1	Peptide interacting with anti-apoptotic proteins of the bcl-2 family
2	Methods of screening of PP1-interacting polypeptides or proteins, peptides inhibiting PP1c binding to Bcl-2 proteins, Bcl-xL and Bcl-w, and uses thereof
3	Mammalian pro-apoptotic bok genes and their uses
4	Amine derivatives for the treatment of apoptosis
5	Mammalian pro-apoptotic Bok genes and their uses
6	Pharmaceutically active pyrrolidine derivatives as Bax inhibitors
7	Mammalian pro-apoptotic Bok genes and their uses
8	Amine derivatives for the treatment of apoptosis
9	Mammalian pro-apoptotic Bok genes and their uses
10	Mammalian pro-apoptotic Bok genes and their uses
11	Mammalian pro-apoptotic Bok genes and their uses
12	Mammalian pro-apoptotic Bok genes and their uses

	Document ID	Kind Codes	Source	Issue Date	Pages
1	US 20070154962 A1		US-PGPUB	20070705	41
2	US 20070059831 A1		US-PGPUB	20070315	68
3	US 20060263368 A1		US-PGPUB	20061123	123
4	US 20060178330 A1		US-PGPUB	20060810	157
5	US 20060057109 A1		US-PGPUB	20060316	41
6	US 20060014199 A1		US-PGPUB	20060119	8
7	US 20040235773 A1		US-PGPUB	20041125	52
8	US 20040191844 A1		US-PGPUB	20040930	62
9	US 20040013658 A1		US-PGPUB	20040122	62
10	US 20030225022 A1		US-PGPUB	20031204	88
11	US 20030208037 A1		US-PGPUB	20031106	76
12	US 20030175717 A1		US-PGPUB	20030918	12

	Title
1	Bcl-2 promoted cell death
2	Nucleic acids, polypeptides, compositions, and methods for modulating apoptosis
3	Targeted chimeric molecules for cancer therapy
4	Use of antisense oligonucleotides or siRNA to suppress expression of eIF-5A1
5	Method of using anti-apoptotic factors in gene expression
6	Molecular detection of chromosome aberrations
7	Polymeric oligonucleotide prodrugs
8	Novel fluorogenic or fluorescent reporter molecules and their applications for whole-cell fluorescence screening assays for caspases and other enzymes and the use thereof
9	Method of inducing apoptosis by reducing the level of thiamin
10	Suppression of eIF5A1 expression to prevent retinal ganglion cell death in the glaucomatous eye
11	Novel fluorescence dyes and their applications for whole-cell fluorescence screening assays for caspases, peptidases, proteases and other enzymes and the use thereof
12	Apparatus and method for predicting treatment response of cancer

	Document ID	Kind Codes	Source	Issue Date	Pages
13	US 20030144238 A1		US-PGPUB	20030731	74
14	US 20030064952 A1		US-PGPUB	20030403	58
15	US 20030050272 A1		US-PGPUB	20030313	75
16	US 20020150885 A1		US-PGPUB	20021017	92
17	US 20020106735 A1		US-PGPUB	20020808	40
18	US 7270801 B2		USPAT	20070918	88
19	US 7226927 B2		USPAT	20070605	75
20	US 7217517 B2		USPAT	20070515	84
21	US 7166467 B2		USPAT	20070123	69
22	US 7034144 B2		USPAT	20060425	11

	Title
13	Nucleic acids, polypeptides, and methods for modulating apoptosis
14	Nucleic acids, polypeptides, compositions, and methods for modulating apoptosis
15	Nucleic acids, polypeptides, and methods for modulating apoptosis
16	Novel fluorogenic or fluorescent reporter molecules and their applications for whole-cell fluorescence screening assays for caspases and other enzymes and the use thereof
17	Novel Bcl-2 related proline rich protein (BPR)
18	Fluorogenic or fluorescent reporter molecules and their applications for whole-cell fluorescence screening assays for caspases and other enzymes and the use thereof
19	Substituted 2-aryl-4-arylaminopyrimidines and analogs as activators of caspases and inducers of apoptosis and the use thereof
20	Nucleic acids, polypeptides, and methods for modulating apoptosis
21	Nucleic acids, polypeptides, compositions, and methods for modulating apoptosis
22	Molecular detection of chromosome aberrations

	Document ID	Kind Codes	Source	Issue Date	Pages
23	US 6984718 B2		USPAT	20060110	68
24	US 6759207 B2		USPAT	20040706	87
25	US 6730474 B1		USPAT	20040504	8
26	US 6716851 B2		USPAT	20040406	76
27	US 6506550 B1		USPAT	20030114	62
28	US 6342611 B1		USPAT	20020129	82
29	US 6335429 B1		USPAT	20020101	82

	Title
23	Fluorescence dyes and their applications for whole-cell fluorescence screening assays for caspases, peptidases, proteases and other enzymes and the use thereof
24	Fluorogenic or fluorescent reporter molecules and their applications for whole-cell fluorescence screening assays for caspases and other enzymes and the use thereof
25	Molecular detection of chromosome aberrations
26	Substituted 2-aryl-4-arylaminopyrimidines and analogs as activators or caspases and inducers of apoptosis and the use thereof
27	Method of including apoptosis by reducing the level of thiamin
28	Fluorogenic or fluorescent reporter molecules and their applications for whole-cell fluorescence screening assays for capsases and other enzymes and the use thereof
29	Fluorogenic or fluorescent reporter molecules and their applications for whole-cell fluorescence screening assays for caspases and other enzymes and the use thereof

	Document ID	Kind Codes	Source	Issue Date	Pages
30	US 6248904 B1		USPAT	20010619	66

	Title
30	Fluorescence dyes and their applications for whole-cell fluorescence screening assays for caspases, peptidases, proteases and other enzymes and the use thereof

	L #	Hits	Search Text
1	L1	6072	"bcl-2"
2	L2	0	anti adj apaoptot$3
3	L3	4088	anti adj apoptot$3
4	L4	1455	l1 same l3
5	L5	1145	"BCL-XL" or "BCL-W"
6	L6	310	l4 same l5
7	L7	12	l6 same dimer$2
8	L8	67341	BENETT RAIN GENESTE HICKMAN
9	L9	0	l6 same l8
10	L10	30	l1 same l8